

Supplementary Table S4: Studies reporting clinical cases (with key details) of *Clostridium perfringens*-associated Necrotising Enterocolitis (NEC) since 1970s.

Reporting year	Major findings	Pathology/ disease presentations	Identification technique/ strains identified	Refs
1976	<i>C. perfringens</i> isolated from 6 out of 7 NEC patients	Pneumatosis intestinalis	Culturing/ <i>C. perfringens</i> type A	1
1978	<i>C. perfringens</i> detected in 3 of 4 deceased NEC patients	Severe pneumatosis intestinalis	Culturing/ <i>C. perfringens</i>	2
1984	<i>C. perfringens</i> isolated from 5 NEC patients, 2 died; <i>C. perfringens</i> being the most found pathogen in 50 NEC patients in a 4-year cohort of 375 babies.	Pneumatosis intestinalis, portal venous gas, sepsis	Culturing/ <i>C. perfringens</i>	3
1984	<i>C. perfringens</i> detected in 2 NEC patients	n/a	Culturing/ <i>C. perfringens</i>	4
1985	<i>C. perfringens</i> detected in 10 NEC patients with 78% fatal outcome	n/a	Culturing/ <i>C. perfringens</i>	5
1985	<i>C. perfringens</i> detected in 9 NEC patients with 78% fatal outcome	Intestinal gangrene and extensive pneumatosis intestinalis	Culturing/ <i>C. perfringens</i>	6
1990	<i>C. perfringens</i> was more abundant in 1 out of 4 NEC infants	n/a	Culturing/ <i>C. perfringens</i>	7
2004	Case-control study of 12 pre-term infants. 3 <i>C.-perfringens</i> -positive infants developed NEC later (100%) and eventually died (100%)	n/a	16S rRNA PCR/ <i>C. perfringens</i>	8
2008	Case-control study of 9 NEC patients associated with <i>C. perfringens</i> . Outcomes compared with non- <i>C. perfringens</i> -NEC (n=32): higher mortality (44% vs 7%) and high percentage of portal venous gas (78% vs 25%)	Abdominal distention; bloody stools; pneumatosis intestinalis; portal venous gas	Culturing; multiplex-PCR toxinotyping/ <i>C. perfringens</i> type A	9

Reporting year	Major findings	Pathology/ disease presentations	Identification technique/ strains identified	Refs
2009	<i>C. perfringens</i> isolated from necrotic colon wall of 1 NEC pre-term patient	Abdominal distention; necrotic intestine; pneumatosis intestinalis; multiple perforation; haemolysis	Culturing; Nagler reaction on egg yolk agar	10
2010	<i>C. perfringens</i> isolated from 3 NEC patients (faecal samples)	n/a	Culturing; 16S rRNA PCR; multiplex-PCR toxinotyping/ <i>C. perfringens</i> type A	11
2010	<i>C. perfringens</i> detected from 3 NEC patients (peritoneal fluid samples) who eventually died from multisystem organ failure	Abdominal distention; pneumatosis intestinalis; extensive bowel necrosis	Intra-hospital culturing	12
2015	A 2-year cohort study of 369 pre-term infants. Overabundant <i>C. perfringens</i> were detected in 4 NEC (Bell 2/3) patients before disease onset (in a total of 12 NEC patients) using NGS technology	n/a	16S rRNA metagenomics (V3-V5 regions); culturing and MALDI-TOF; multiplex-PCR toxinotyping/ <i>C. perfringens</i> type A, 3 isolates harboured β2-toxin	13
2016	A case-control study of 3 NEC patients. <i>C. perfringens</i> were found to be significantly more abundant from meconium to NEC onset.	Pneumatosis intestinalis and/or portal venous gas	16S rRNA metagenomics (V3-V4 regions)	14

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